世界华人消化杂志 2014年8月28日; 22(24): 3600-3607
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

文献综述 REVIEW

以胰腺为靶点治疗糖尿病的相关信号通路

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■背景资料
目前针对胰岛治疗糖尿病的药物主要通过促进胰岛素分泌, 控制胰高血糖素释放来降低血糖, 而胰岛β细胞凋亡直接影响胰岛素的分泌量, 胰岛β细胞凋亡与众多信号通路相关, 通过分析论述以胰腺为靶点的与糖尿病相关的信号通路, 对基础研究、新药研发、临床治疗都有重要意义.

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上海市科学技术委员会科研计划基金资助项目, No. 12401903204
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收稿日期: 2014-02-24 修回日期: 2014-03-20
接受日期: 2014-04-04 在线出版日期: 2014-08-28

Pancreatic signal pathways potentially used as targets for treatment of diabetes

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Received: 2014-02-24 Revised: 2014-03-20
Accepted: 2014-04-04 Published online: 2014-08-28

Abstract
The pancreas is the main place where pathological changes of diabetes occur, and inflammation and oxidative stress can interfere with various cell signaling pathways, causing pancreatic lesions and diabetes. Therefore, the pancreas is an important target for the treatment of diabetes. This paper will discuss pancreatic signaling pathways potentially used as targets for the treatment of diabetes in terms of promotion of insulin secretion, inhibition of glucagon secretion, and suppression of islet beta cell apoptosis. The research of these signaling pathways is important for elucidating the pathogenesis of diabetes and developing more safe and effective new drugs. ATP sensitive potassium channel and glucagon like peptide-1 (GLP-1) receptor signaling pathways are associated with insulin secretion and have been widely used as therapeutic targets. The signaling pathway mediated by G protein coupled receptors is a hot spot of diabetes research in recent years, and other signaling pathways are being studied.

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Key Words: Diabetes; Pancreas; Signaling pathways; Target

Lin YF, Shen WD. Pancreatic signal pathways potentially used as targets for treatment of diabetes. Shijie Huaren Xiaohua Zazhi 2014; 22(24): 3600-3607 URL: http://www.wjgnet.com/1009-3079/22/3600.asp DOI: http://dx.doi.org/10.11569/wcjd.v22.i24.3600

摘要
胰腺是糖尿病主要的病变场所, 炎症、氧化应激等都会干扰各种细胞信号通路的传导, 引起胰腺组织病变而导致糖尿病, 胰腺是治疗糖尿病的重要靶点. 本文从促进胰岛素分泌、抑制胰高血糖素分泌、抗胰岛β细胞凋亡3个方面着手, 阐述以胰腺为靶点治疗糖尿病的相关信号通路, 这些信号通路的研究对阐明糖尿病发病机制及研发更安全有效的新药具有重要意义. 与胰岛素分泌有关的ATP敏感性钾通道和胰高血糖素样肽1(glucagon like peptide-1)受体信号通路作为治疗靶点已被广泛运用于临床, G蛋白偶联受体介导的信号通路是近年来研究的热点, 其他信号通路还在不断的研究中, 更多更好的临床药物是值得期待的.

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关键词: 糖尿病; 胰腺; 信号通路; 靶点

核心提示: 以胰腺为靶点治疗糖尿病的相关各信号通路主要分为促进胰岛素分泌、抗胰岛β细胞凋亡, 同时抑制胰高血糖素分泌3个方面, 且不同信号通路之间各有特点又存在很多相互关联.

林玉芳, 沈卫东. 以胰腺为靶点治疗糖尿病的相关信号通路. 世界华人消化杂志 2014; 22(24): 3600-3607 URL: http://www.

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wjgnet.com/1009-3079/22/3600.asp DOI: http://dx.doi.org/10.11569/wcjd.v22.i24.3600

0 引言

糖尿病是一种内分泌性炎症性疾病, 目前对糖尿病的治疗也体现出一种多通路、多靶点的调控方式. 胰腺是糖尿病主要的病变场所, 也是治疗糖尿病的重要靶点, 针对胰腺组织治疗糖尿病主要体现在促进胰岛素分泌、抑制胰高血糖素分泌、抗胰岛β细胞凋亡几个方面, 以下就以胰腺组织作为靶点治疗糖尿病的相关信号通路进行综述.

1 促进胰岛素分泌

1.1 Ca^{2+}通道和ATP敏感性钾通道 胰腺β细胞是一种电兴奋性内分泌细胞, 而β细胞分泌胰岛素是由胞内Ca^{2+}浓度升高直接触发的, Ca^{2+}通道和ATP敏感性钾通道(ATP-sensitive potassium channel, KATP)活性的改变对胞内钙浓度及胰岛素的分泌都起到关键作用. 其中L型钙通道是葡萄糖诱导的胰岛素分泌的重要通道, 其变异性容易导致2型糖尿病(type 2 diabetes mellitus, T2DM)[1]. 能量代谢状态则对KATP通道的电活动会产生影响. 在生理状态下, 当葡萄糖升高到一定浓度时, 葡萄糖进入β细胞内代谢产生能量, 生成的ATP会使细胞膜上的 KATP通道关闭, 膜去极化, 从而诱发动作电位, Ca^{2+}通道开放, 使胞外钙内流, 胞浆内的Ca^{2+}浓度升高, 促使胞内钙库释放钙, 胞浆中Ca^{2+}浓度急剧升高, 从而启动胰腺β细胞分泌胰岛素[2]. 因此, Ca^{2+}通道和KATP通道可以作为治疗T2DM的药物作用靶点. 磺酰脲类药物是通过关闭胰岛细胞的ATP敏感性钾通道而发挥降血糖作用的, 但容易导致低血糖和体质量增加[3], 非磺酰脲类药物如米格列奈的半衰期较短, 主要针对餐后高血糖, 与磺酰脲类药物相比, 可以避免严重低血糖现象发生.

1.2 β细胞GLP-1受体信号通路 胰高血糖素样肽1(glucagon like peptide-1, GLP-1)是一种主要由远端回肠、直肠和结肠的L细胞分泌的葡萄糖浓度依赖的多肽激素, 他不仅能作用于胰岛β细胞刺激胰岛素的基因表达、蛋白质合成和分泌, 还可以作为一种生长因子促进胰岛素分泌细胞增殖, 抑制其凋亡.

GLP-1受体主要定位在胰腺组织中, 当GLP-1与其受体结合后, 可激活腺苷酸环化酶(adenylate cyclase, AC), 使胞内环腺苷酸(cyclic adenosine monophosphate, cAMP)增加, cAMP再激活下游的蛋白激酶A(protein kinase A, PKA)和交换蛋白(exchange protein directly activated by cAMP, EPAC). β细胞中GLP-1就是经由PKA和EPAC途径激活Ca^{2+}信号通路和促进胰岛素释放的[4,5]. 此外, GLP-1受体还可经由基质金属蛋白酶9或表皮生长因子β细胞素反式激活表皮生长因子受体(epithelial growth factor receptor, EGFR)[6], EGFR再激活磷脂酰肌醇3激酶(phosphatidyl inos-itol3-kinase, PI3K)及其下游的PKB/Akt和丝裂原活化蛋白激酶P38[6,7], 以调节影响胰岛素分泌的一些重要基因的表达. GLP-1还可以通过上调抗凋亡蛋白板层素相关多肽2和Bc-l2, 激活核因子κB(nuclear factor-κB, NF-κB)启动子的活性等途径, 确保胰岛素分泌细胞的存活. 生理状况下, 体内分泌的GLP-1半衰期很短, 极易被二肽基肽酶Ⅳ(dipeptidyl peptidase Ⅳ, DDP-Ⅳ)降解, 不能被人体有效地利用. 但是, 人们研究出了长效GLP-1类似物、DPP-Ⅳ抑制剂, 如利拉鲁肽、西格列汀等, 这些药物治疗糖尿病也取得了非常好的疗效[8]. 在一项为期2年的安全性分析中, T2DM老年患者服用西格列汀100 mg/d的剂量进行治疗具有良好的耐受性, 且无不良反应[9]. 西格列汀通过增加血浆GLP-1水平和峰值应力, 还可促进心肌葡萄糖摄取, 增强射血分数、二尖瓣环收缩期速度, 和局部缺血性左心室功能, 改善心肌缺血耐受[10].

1.3 经典Wnt信号通路 经典Wnt信号通路又称Wnt/β-catenin信号通路, β-catenin是这条信号通路的效应因子. Wnt信号可与细胞表面受体Frizzled和低密度脂蛋白受体相关蛋白5/6(low density lipoprotein receptor related protein 5/6, LRP5/6)结合, 激活胞内蓬乱蛋白(dishevelled, Dsh). 激活的Dsh促进胞质内糖原合成酶激酶3β(GSK3β)、结肠癌抑制因子(adenom atous polyposis coli, APC)及支架蛋白(axin)与β-catenin形成的降解复合体解体, 抑制β-catenin磷酸化, β-catenin从胞质转位至核内, 与 T细胞因子(T cell factor, TCF)/淋巴增强因子(lymphoid enhancer factor, LEF)相结合, 形成转录复合体激活细胞周期蛋白D1(*cyclinD1*)、*c-Myc*等靶基因的表达[11].

大量研究表明, 经典Wnt信号通路调控因子基因*TCF7L2*的多态性与T2DM风险具有相关性, TCF7L2编码经典Wnt信号通路下游的重要转录调控因子TCF4. 而胰高血糖素原基因是经典Wnt信号通路的一个靶基因, 经典Wnt信号通

■研发前沿
与胰岛素分泌有关的ATP敏感性钾通道和GLP-1受体信号通路作为治疗靶点已被广泛运用于临床, G蛋白偶联受体介导的信号通路是近年来研究的热点, Wnt信号通路、MAPK信号转导通路等与糖尿病的关系也有较多研究, 开发更好的临床药物是研究各种信号通路的目的所在.

■相关报道
McCormick等发现西格列汀可通过增加血浆GLP-1水平和峰值应力, 促进心肌葡萄糖摄取, 增强射血分数、二尖瓣环收缩期速度, 和局部缺血性左心室功能, 改善心肌缺血耐受. 说明该药对糖尿病及冠心病都有很好的治疗作用.

路激活可促进胰高血糖素原基因表达*GLP-1*[12]. TCF7L2多态性可能通过调控GLP-1的表达来增加T2DM的风险. *TCF7L2*基因突变会促进TCF4表达, TCF4过度表达可抑制经典Wnt信号通路下游的转录活性[13], 在T2DM中还发现β-catenin浓度的明显降低[14], 都会导致GLP-1诱导的胰岛素分泌减少, 加速糖尿病发展. 此外, Wnt通路对调节胰岛β细胞功能和质量起着举足轻重的作用[15]. 激活经典Wnt信号通路还可以促进胰腺β细胞的增殖. TCF7L2多态性可能还通过影响β细胞增殖和功能, 进而影响胰岛素分泌来诱发T2DM.

1.4 G蛋白偶联受体介导的信号通路 G蛋白偶联受体(G protein-coupled receptors, GPCRs)是体内最大的膜受体超家族, 主要通过G蛋白介导生物效应. 其中与胰岛素分泌相关的GPCRs主要是GPR40、GPR119、GPR120, 其中以GPR40研究最多.

GPR40主要在胰腺组织中高表达, 是中长链脂肪酸的受体, 其通过耦合G蛋白中的Gi/o家族开始启动信号传导, 通过激活磷脂酶C(phospholipase C, PLC), 把磷酸肌醇4, 5-磷酸(phosphatidylinositol-4, 5-bis-phosphate, PIP-2)分解, 生成了1,4,5-三磷酸肌醇(inositol 1,4,5-triphosphate, IP3), 刺激内质网钙离子释放. GPR40还可通过提高胞内cAMP浓度, 延迟整流性K^+通道失活, 延长细胞去极化, 使Ca^{2+}进入细胞, 细胞内Ca^{2+}浓度迅速增加, 触发胰岛素颗粒释放[16-20]. 且近年来报道了数10种人工合成的GPR40激动剂, TAK-875和AMG-837是首批进入临床实验的GPR40激动剂. GPR40激动剂如TAK-875促胰岛素分泌具有葡萄糖依赖性, 且不会引起低血糖反应[21]. TAK-875降低空腹和餐后血糖及HbA1c疗效与格列美脲相当[22].

GPR119在胰腺组织及胃肠道中都有表达, 可被溶血磷脂胆碱和油酰乙醇胺激活, 其下游中有信号传递至GPRs的q亚基, 并使胞内cAMP水平升高而发挥相应作用[23]. GPR119也可通过促进肠道GLP-1分泌, 间接促进胰岛素分泌. GPR120在脂肪组织中高表达, GPR120的激活促进GLP-1分泌[24], 间接促进胰岛素分泌.

2 改善胰岛α细胞胰岛素信号通路减少胰高血糖素分泌

胰高血糖素是胰岛α细胞分泌的多肽类激素, 胰高血糖素分泌亢进及功能紊乱在T2DM的病理机制中占有重要的作用[25]. 生理情况下, β细胞分泌的胰岛素通过旁分泌作用抑制α细胞分泌胰高血糖素. 研究发现, α细胞上同样有胰岛素受体(insulin receptor, IR)、胰岛素受体底物-1/2(insulin receptor substrate-1/2, IRS-1/2)及PI3K的表达, 胰岛素通过IRS-1-PI3K途径来抑制胰岛α细胞胰高血糖素的基因表达和释放[26,27]. Tsuchiyama等[28]研究指出: T2DM中高胰高血糖素分泌的机制主要是由于α细胞胰岛素抵抗, 导致α细胞分泌亢进. 而运用噻唑烷二酮类药物和GLP-1[29]能改善胰岛素抵抗, 抑制胰高血糖素分泌. 此外, 胰高血糖素原是胰高血糖素的前体物质, 抑制胰高血糖素原向胰高血糖素表达, 也可间接抑制胰高血糖素分泌. 总之, 通过改善胰岛α细胞胰岛素抵抗、减少胰高血糖素分泌有望成为治疗糖尿病的新靶点.

3 抗胰岛β细胞凋亡

3.1 MAPK信号转导通路 MAPK信号转导通路是哺乳动物细胞内介导细胞反应的重要信号系统, 参与细胞增殖、生长、分化及凋亡等多种细胞行为的调控[30]. 已发现在真核细胞中存在4条MAPK信号转导通路, 即ERK通路、JNK通路、P38通路和ERK5通路. 不同的细胞外刺激可使用不同的MAPKs信号通路, 通过其相互调控而介导不同的细胞反应. 细胞应激及细胞炎症因子主要激活JNK、P38通路[31-33]. 研究表明, 链蠕孢素可通过减少丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)的磷酸化及其上游激酶活性来抑制炎症反应, 达到对1型糖尿病的预防作用[34].

3.1.1 JNK通路: c-Jun氨基末端激酶(c-Jun N-terminal kinase, JNK)是一类丝氨酸/苏氨酸蛋白激酶, 也被称为应激活化蛋白激酶, 是MAPK的家族成员之一, 他共有3个JNK基因, *JNK1-3*. JNK通路的关键激酶包括MAPKK类的MEK4、MEK7和MAPKKK类的MEKKI/2/3/4. JNK信号通路的模式可大致总结为: 应激、紫外线等→生发中心激酶(germinal center kinase, GCK)→MEKK→MEK4/7→JNK→细胞凋亡、增殖、分化等[35]. 在静止细胞中, JNK定位于细胞浆与细胞核. JNK能通过转录因子途径和线粒体途径介导多种胞外刺激如应激、Fas、肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)等诱导的细胞凋亡.

当被刺激因素激活后, 胞质中一部分活化的JNK能够直接磷酸化激活胞质中促凋亡蛋白

Bax[36]、抑制Bcl-2等抗凋亡蛋白[36,37]. 活化的Bax再转位至线粒体外膜, 使其通透性增加而释放促凋亡线粒体蛋白[38], 进而介导线粒体途径的细胞凋亡. 胞质中另一部分活化的JNK就转位到细胞核中, 使核内底物磷酸化, 发挥生物学效应, 如通过磷酸化而激活转录因子激活蛋白1(activator protein-1, AP-1)(如c-Jun、c-Fos等)、激活转录因子2(activating transcription factor-2, ATF-2)等, 从而调节下游的凋亡相关靶基因的转录和凋亡蛋白的表达[36, 39-41]. 活化的JNK进入细胞核激活相应转录因子后还可诱导Bim、Bid等BH3-only蛋白表达, 从而使Bax等促凋亡蛋白活化, 活化的Bax再从胞质转入线粒体, 破坏线粒体膜通透性, 致细胞色素C等促凋亡物质的释放而介导线粒体途径的细胞凋亡[42].

1型糖尿病及T2DM后期主要的发病机制都涉及胰腺β细胞的凋亡, JNK信号通路在胰腺β细胞凋亡过程中发挥了重要作用[43]. 促炎性因子白介素-1β(interleukin-1β, IL-1β)、干扰素c(interferon-C, IFN-C)等是白细胞介导的β细胞损伤和凋亡的主要诱因, 在动物实验中, 当阻断JNK信号通路后能抑制IL-1B诱导的β细胞凋亡[44]. Fukuda等[45]则报道了剔除*JNK1*基因后可显著下调MLD-STZ诱导的高血糖症模型小鼠的血糖水平, 提示JNK通路介导了MLD-STZ诱导胰腺β细胞凋亡进而导致高血糖症的产生. 因此, JNK信号通路可以作为抗胰腺细胞凋亡治疗糖尿病的一个重要调节靶点.

3.1.2 P38通路: p38MAPK作为MAPK信号转导通路的成员之一, 广泛参与细胞增殖、分化及凋亡等多种细胞功能的调控. p38MAPK的激酶级联为: 促分裂原活化蛋白激酶的激酶的激酶(包括MEKK124、MLK2/3、DLK、ASK1、Tpl2和Tak1)-促分裂原活化蛋白激酶的激酶(MEK3/MEK6, 又称MKK3/MKK6)-p38[46]. 哺乳动物p38MAPK有4种亚型分别是p38A、p38B、p38C(ERK6, SAPK3)、p38D(SAPK4), 其中p38D在胰岛β细胞中的表达水平较高.

糖尿病状态下的高糖-蛋白激酶C通路、氧化应激、糖基化终产物等都可激活MAPK家族, 可使p38MAPK水平升高, 导致胰岛β细胞功能紊乱和凋亡[47]. 胰岛素突变体蛋白2的表达也可激活ask1-p38通路, 通过诱导内质网应激并引起小鼠胰腺β细胞死亡. 删除ASK1则可减轻胰岛素突变体蛋白2引起的胰腺β细胞死亡并延迟小鼠糖尿病的发生. 此外, p38抑制剂也能抑制胰岛素突变体蛋白2诱导的胰腺β细胞系细胞死亡, 提示ask1-p38通路的抑制可成为各种类型的糖尿病的一种有效治疗方法[48]. Sumara等[49]则采用缺乏p38D的小鼠模型和相应的野生型对照小鼠模型进行研究, 发现p38D在胰腺器官的表达与血糖稳态相关. 在禁食16 h后, 二者的胰岛素的敏感性相同, 但缺乏p38D的小鼠相对于野生型小鼠的血糖结果提示糖耐量明显改善, 葡萄糖刺激缺乏p38D的小鼠后获得了较低的血糖水平和较高的血清胰岛素水平. 进一步的研究中, Sumara等[49]分离了二者的胰岛β细胞, 并检测他们在体外分泌胰岛素的能力, 发现二者胰高血糖素的释放程度相同, 但缺乏p38D的小鼠胰岛相比野生型小鼠胰岛释放更多的胰岛素, 提示p38D缺乏可以通过直接刺激β细胞来改善葡萄糖耐量, 增加胰岛素分泌, 且这种胰岛素分泌并不依赖ATP敏感性钠通道及钙通道的开放. p38D可降低蛋白激酶D1(protein kinase D1, PKD1)的活性, 抑制PKD1指导进行胞吐的反式高尔基体网(trans-golgi network, TGN)的胰岛素囊泡的分裂, 从而减低胰岛素的分泌, 表明p38D-PKD1通路是调节胰腺β细胞胰岛素胞吐的关键调控因素, 也是MAPK信号转导通路中调节胰岛素释放及胰腺β细胞凋亡[50]的关键靶点之一.

3.2 NF-κB通路 NF-κB可促进DM的β细胞凋亡, 引起胰岛素分泌减少, 在糖尿病发生中亦有重要作用[51]. 他存在于所有哺乳动物的细胞中, 通过与一系列基因的上游启动子或增强子内部的κB序列特异性结合而调节这些基因的表达[52]. 哺乳动物NF-κB家族共有5个成员, 分别是NF-κB1、NF-κB2、p65(RelA)、RelB、C-Rel. IκB是NF-κB的抑制蛋白, 在通常情况下, IκB与NF-κB结合, 形成无活性的复合物, 存在于胞浆中. 细胞因子如TNF-α、IL-1β、干扰素γ(interferon-γ, IFN-γ)、一氧化氮(nitric oxide, NO)及活性氧簇(reactive oxygen species, ROS)等外界因素可刺激细胞, 细胞产生蛋白激酶使IKKβ磷酸化, IKK被激活而降解IκB, 从而使NF-κB活化进入核内, 调控炎症反应和免疫应答相关基因的表达[53].

NF-κB活化与β细胞凋亡密切相关. Heimberg等[54]研究发现在离体条件下, NF-κB活化是β细胞凋亡的前兆. β细胞的凋亡部分是依赖NF-κB介导的通路活化引起的[55]. NF-κB通过削弱β细胞功能及促进β细胞凋亡, 减少血清胰岛素含量使血糖升高, 导致糖尿病发生. 而在鼠胰岛

■创新盘点

针对糖尿病的相关信号通路有较多报道, 本文针对胰岛为靶点治疗糖尿病有关的各类信号通路做系统阐述, 有助于读者系统的了解各信号通路的特点和异同及相互联系.

■应用要点
本文系统的阐述了以胰腺为靶点治疗糖尿病的所有相关信号通路, 对指导新药开发及临床各类药物的对比运用都有一定指导意义. 目前针对很多信号通路的药物研究尚处于初级阶段, 需要更多基础理论知识的指导.

中, 用NF-κB特异性寡脱氧核酸来阻断四氧嘧啶引发的NF-κB活化, 可以预防糖尿病发生[56]. 因此, 通过阻断依赖NF-κB的信号通路来对抗β细胞凋亡, 可以成为防治DM的新靶点. 但是, IL-1β等在介导NF-κB活化促进β细胞凋亡时, 也促进了锰超氧化物歧化酶(Mn-SOD)、热休克蛋白(Hsp)70、*Hsp27*等基因的表达, 增强β细胞的修复功能, 一定程度上对抗了β细胞凋亡[53]. 或许NF-κB活化介导的促凋亡和抗凋亡之间的平衡才是保证β细胞功能正常的因素.

3.3 mTORC1-S6K1信号通路 哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)是在哺乳动物中发现的一个高度保守的丝氨酸/苏氨酸蛋白激酶, 属于磷酯酰肌醇激酶相关激酶(phosphatidylinositol kinase-related kinase, PIKK)超家族成员, 其作用与细胞调节, 增生调控和癌细胞新陈代谢有关. 在哺乳动物中, mTOR以两种复合物的形式存在, mTOR Complex1及mTOR Complex2. mTOR活性也受多种调节信号的影响, 结节性硬化复合体1/2(tuberous sclerosis complex1/2, TSC1/TSC2)是mTOR最重要的上游信号分子, 调控mTOR活性的主要上游信号通路包括PI3K-Ak-tTSC1/2-mTOR信号通路和LKB1-AMPK-TSC1/2-mTOR信号通路[57], 他们都主要通过TSC发挥调控mTOR的作用. 核糖体蛋白S6激酶1(ribosomal protein S6 kinase l, S6K1)是mTOR信号通路下游的主要效应蛋白, 是一个属于AGC激酶家族的Ser/Thr激酶. S6K1的活性主要取决于其残基的功能.

目前认为PI3K-Akt-TSC1/2-mTORC1-S6K1信号通路主要在胰岛素信号传导及胰岛素抵抗中发挥主要作用, 但是也有研究表明其在介导胰腺β细胞凋亡中也发挥作用. 胰岛素受体底物-1的丝氨酸磷酸化是引起胰岛素抵抗的主要机制[58], 而在促进β细胞凋亡中, 该通路同样是通过mTOR-S6K1介导IRS-2 Ser/Thr磷酸化, 进而促进IRS-2降解而导致的[59]. mTOR特异性抑制剂雷帕霉素可通过抑制IRS-1/2丝氨酸残基磷酸化, 从而改善胰岛素敏感性、抑制β细胞凋亡[60-63]等.

此外, 微小RNA-7/7a(microRNA-7/7a, miR-7/7a)也作为mTOR信号通路的组成部分, 抑制miR-7a可激活mTOR信号从而促进成年小鼠原代胰岛β细胞的复制, 这一效果可被mTOR抑制剂雷帕霉素逆转, 说明miR-7可作为成人β细胞增殖的开关, 并且miR-7-mtor增殖轴保留在人体最初的β细胞中, 可成为糖尿病的治疗目标[64].

3.4 “HIF-1α-Bcl-xL等分子-凋亡”通路 缺氧诱导因子-1α(hypoxia-inducible factor 1-alpha, HIF-1α)具有氧浓度敏感性, 通过核定位序列介导入细胞核, 与HIF-1β二聚化, 形成具有转录活性的异二聚体HIF-1, 发挥转录因子作用[65], 参与低氧适应、血管生成、免疫应答、细胞凋亡等多种反应[66].

研究显示HIF-1α在糖尿病中表达下调, 且功能异常. Bcl-2家族的Bcl-xL、MCL-1和IAP家族的Survivin等重要的抗凋亡成员, 是HIF-1α下游重要的凋亡调控分子[67]. 糖尿病中HIF-1α蛋白水平下调和功能障碍直接导致上述抗凋亡分子表达降低, 最终导致β细胞凋亡, 是糖尿病发生与进展的重要环节. 研究显示, 糖尿病患者胰岛细胞β细胞中Bcl-xL表达明显降低, 同时伴随β细胞凋亡[68]. 而活化Akt信号所致Bcl-xL高表达则抑制β细胞凋亡和糖尿病发生[69]. 由此可见, Bcl-xL是β细胞凋亡的关键分子. HIF-1α的异常导致糖尿病患者Bcl-xL表达水平下调, 从而促进β细胞凋亡. “HIF-1α-Bcl-xL等分子-凋亡”通路异常, 在糖尿病的发生与进展过程中发挥重要作用, 也可以作为治疗糖尿病的新靶点.

4 结论

胰岛β细胞的数量及其分泌胰岛素能力在糖尿病的发生和发展中具有重要意义, 促进胰岛素分泌、抗胰岛β细胞凋亡, 同时抑制胰高血糖素分泌是针对胰腺组织治疗糖尿病的主要思路. 随着在分子、基因等水平对糖尿病病因、病理机制的不断认识, 治疗糖尿病的通路和靶点也在不断的研究发掘, 以上信号通路在诱发和治疗糖尿病的机制各有不同, 都为糖尿病的治疗提供了不同的思路和方法. 其中, 与胰岛素分泌有关的ATP敏感性钾通道和GLP-1受体信号通路作为治疗靶点已被广泛运用于临床, G蛋白偶联受体介导的信号通路是近年来研究的热点, 其他信号通路还在不断的研究中, 更多更好的临床药物是值得期待的, 临床上应该根据患者的具体症状进行个体化选择治疗. 此外, 很多信号通路之间都有交汇点, 可以产生相互反应扩大和增强信号作用, 同时在很多信号通路中, 往往又会产生相反的两种调节作用, 正反调节作用的平衡或许才是胰岛细胞功能正常的保证. 对不同信号通路的认识都涉及到较深入的分子、基因水平, 但是仍然有很多分子机制不明

确, 进一步的研究和阐明不同信号通路的机制及相互反应, 对研究和治疗糖尿病都会有很大的帮助. 此外, 西药治疗糖尿病以单通路单靶点为主, 针对不同信号通路的异常, 中医中药及针灸的多靶点多通路调节作用显示出明显的优势, 而中药及针灸治疗糖尿病的效应机制有赖于通过上述各种信号通路进行阐明, 中医针灸的效应机制研究也将更多趋于分子、基因水平.

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■名词解释

哺乳动物雷帕霉素靶蛋白(mTOR): 在哺乳动物中发现的一个高度保守的丝氨酸/苏氨酸蛋白激酶, 与细胞增生调控和癌细胞新陈代谢有关;

缺氧诱导因子-1(HIF-1α): 具有氧浓度敏感性, 通过核定位序列介导入细胞核, 参与β细胞凋亡.

■同行评价
文章内容以科学性理论性知识为主, 添加一些近期的相关基础及临床研究报道, 方便读者对胰腺为靶点治疗糖尿病的相关信号通路的系统认识.

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编辑 郭鹏 电编 闫晋利

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton,
CA 94588, USA
Fax: +1-925-223-8242
Telephone: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
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ISSN 1009-3079

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